Development of overweight in adolescence

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Chapter 3

Periods of infancy and childhood growth affecting adiposity at age 16 years

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ABSTRACT

Objective: To assess in which period during infancy and childhood, growth is most associated with overall and abdominal adiposity in adolescence, and with associated metabolic traits. Furthermore, we aimed to assess if these associations differ depending on smoking during pregnancy.

Population & methods: We obtained repeated anthropometric measurements from birth to mean age of 16.2 years on 772 girls and 708 boys in a population-based cohort. At age 16.2 years, weight, height, skinfold thicknesses, %BF, waist circumference, blood pressure, glucose, insulin, and lipids were measured.

Results: Weight gains between age 2 to 4 and age 4 to 7 years were most strongly associated with higher BMI, sum of skinfolds, %BF and waist circumference at age 16.2 years. Increases were +1.01 to +1.42 SDs per SD in weight gain (all $p<0.001$). Increases in risks of being overweight or obese at age 16.2 years (odds ratios) were 23.9 to 32.5 per SD in weight gain ($p<0.001$). Gains in these periods were also associated with a less favorable metabolic syndrome score. If mothers smoked during pregnancy, these weight gains were stronger associated with adiposity measurements at age 16.2 years (0.33 – 0.38 SDS higher; all $p<0.05$) than if mothers did not smoke during pregnancy.

Conclusions: Strong increases in weight SDS from ages 2 to 7 years predispose to overall and abdominal adiposity and their associated metabolic traits in adolescence. In adolescents whose mothers smoked during pregnancy, associations with weight gain during these years is even more pronounced.

INTRODUCTION

Overweight is associated with an increased risk of cardiovascular morbidity, such as diabetes, hypertension, and dyslipidemia. These problems start early in life. It has been hypothesized that critical time periods exist in which accelerated growth constitutes a risk factor for subsequent adiposity and its associated metabolic complications.[1] Specifically, these include gestation, early infancy, the period of adiposity rebound, and adolescence. Systematic reviews have focused mainly on rapid weight gain in infancy (from birth to 2 years of age).[2-4] These concluded that although populations, definitions of exposure and outcome variables, and included confounders varied greatly, consistent positive associations of rapid infant (or early childhood) growth with subsequent overweight in adolescence and adulthood were found. The period of adiposity rebound, i.e. between ages 4 to 7 years, has also been described as important in the development of overweight in later life.[5] Timing of the adiposity rebound is associated with adult overweight, independent of the BMI at the start of the adiposity rebound.[5]

It is difficult to evaluate which of these critical time periods is most important both from a practical and from a statistical point of view. Contemporary cohorts in which longitudinal data in childhood and adolescence have been obtained are scarce; and most of the studies on rapid growth have concentrated on infant weight gain without taking further childhood weight gain into account.[6] Moreover, most of the studies that evaluated multiple anthropometric measurements used BMI as outcome measure. Although BMI is easy to obtain and very reliable, it does not differentiate between lean body mass and fat mass.[7] It has been suggested that rapid weight gain especially leads to increased fat mass.[8] From a statistical point of view, collinearity is an intrinsic problem, rendering it impossible to simply adjust growth during adjoining periods for each other to evaluate which period is most important.[9] Moreover, the association between rapid weight gain in childhood and subsequent adiposity may be affected by other variables, either confounders, e.g. socioeconomic status (SES) and pubertal stage, or effect modifiers, e.g. smoking during pregnancy.[2,10] If such an effect modification exists, it may have important additional consequences for targeting of preventive measures to high-risk groups.

The primary aim of our study was to assess in which period during infancy and childhood growth is most associated with overall and abdominal adiposity in adolescence, and with associated metabolic traits. Furthermore, we aimed to assess if these associations differ dependent on smoking during pregnancy.

METHODS

Study population

Our study was performed in the TRAILS cohort (n=2230).[11] Children were recruited through community registers and schools to obtain a representative sample of the three northern provinces of the Netherlands. Three assessment visits, which included weight and height measurements, have been performed in 2001-2002, 2003-2004 and 2005-2007, at mean ages (± SD) of 11.1 ± 0.6, 13.5 ± 0.6, and 16.2 ± 0.7 years, respectively. Data on previous growth were collected of 1669 participants, which represent 74.8% of the cohort. Reasons for attrition were that records could not be traced (n=239, 10.7%) or that consent of participants to extract these data lacked (n=322, 14.4%). We only included children of whom growth data were available and who participated in all TRAILS assessment visits (n=1593) and we excluded children born prematurely (gestational age <37 weeks, n=90) and children whose gestational age was unknown (n=23), resulting in a population of n=1480. All procedures were approved by the Dutch Central Committee on Research Involving Human Subjects (CCMO). Written informed consent was obtained from parents or custodians.

Measures

Weight and height

All infant and childhood growth data, including birth weight and length reported by parents, were extracted from records of the well-child clinics. These clinics are attended by 95% of the Dutch population. Children attend at 1, 2, 3, 4, 6, 9, 11, 14, and 18 months, and at 2, 3, 4, 5, 10, and 13 years of age. During all visits weight and length/height were measured by trained nurses.[12-14] At the TRAILS assessment visits, weight was measured with a calibrated scale (Model 770, Seca, Hamburg, Germany) and height with a calibrated stadiometer (Model 214, Seca, Hamburg, Germany). In total, 18 (IQR, 14-21) measurements of weight and height were available per participant.

From weight and length/height, BMI was calculated in kg/m^2. We defined overweight and obesity according to international age- and sex-adjusted BMI criteria.[15]

Measures of abdominal adiposity and associated metabolic traits

At a mean age of 16.2 years, triceps, biceps, subscapular, and supra-iliac skinfold thicknesses were obtained with a Harpenden skinfold caliper (CMS instruments, London, UK), from which we calculated sum of four skinfolds. Waist circumference was measured midway between the lower costal margin and the iliac crest. We performed all measurements in duplicate; and if the difference between these measurements exceeded a predefined value, a third measurement was performed. All available measurements were used to

calculate means. We performed hand-to-foot bioelectrical impedance analysis (BIA 101, Akern®, Italy) to calculate %BF with the use of the Deurenberg equation.[16]

SBP and DBP were measured in duplicate with the use of a Dinamap Critikon 1846SX (Critikon Inc., Tampa, FL, USA) and the mean of the two readings was calculated. Glucose, insulin, LDLC, and HDLC were determined from a fasting blood sample according to standard laboratory procedures.

Covariates

Information on smoking during pregnancy was obtained by parental questionnaires at age 11.1 years, which showed good agreement with data from the well-child clinics.[17] We used parental questionnaire data in our analyses, because less data were missing. At age 16.2 years, questionnaires were filled out by child and parents on pubertal stage (Physical Development Scale questionnaire),[18] ethnicity, and SES. SES was calculated as the mean of SDSs on family income, mother's and father's level of education and occupation based on the International Standard Classification of Occupations.[19] The 25% lowest, 50% intermediate, and 25% highest were considered to represent low, medium, and high SES, respectively.

Data analysis

Weight, BMI, skinfolds, waist circumference, SBP, insulin, and triglycerides were ln-transformed to obtain a better approximation of the normal distribution, before calculating age- and sex-specific SDSs with the use of means and standard deviations. Analyses using SDSs calculated according to a national reference population (available only for BMI, skinfolds, and waist circumference)[20,21] provided similar results to analyses using the SDSs calculated within our own population. We decided to present results from analyses using these latter SDSs because this was applicable to all outcome measures.

All available weight and BMI data were standardized and used to construct growth curves from birth to age 18 years, because many participants were measured after the mean age of 16.2 years (n=570, 40.9%). Based on previous literature,[1,22-25] time intervals were defined as birth to 6 months, 6 months to 1 year, 1 to 2, 2 to 4, 4 to 7, 7 to 11, and 11 to 15 years of age. Growth was analyzed in the SD scale. We assumed that growth is characterized by a straight line within each interval. These lines connect at the breakpoints in age mentioned above and visually resemble a "broken stick".[26] The procedure resulted in 8 estimates per person (1 for each breakpoint in age) which together describe the person's trajectory. Change scores per period were calculated as the difference between the estimates of successive breakpoints in age.

Our first aim was to assess the influence of changes in weight SDS between birth and age 15 years on overall and abdominal adiposity, and their associated metabolic traits. We used linear and logistic regression models to predict BMI, skinfolds, %BF, waist circumference,

SBP, DBP, glucose, insulin, HDLC, LDLC, and triglycerides SD scores, overweight/obesity, and a composite score of the metabolic syndrome[27] at mean age 16.2 years. In all analyses, we entered weight SDS at the end of each age period. Next, we entered change in weight SDS in this age period to estimate the additional effect of weight change during the period. We calculated the increase in variance explained after adding the change in weight to the model. Larger increases in explained variance indicate that growth rate during this age period is more strongly associated with overweight, compared with growth rates in other age periods. Choosing the end of the age period instead of the start disentangles the effect of change in weight SDS and time effect, i.e. the natural progression in correlation that occurs because the end of each age period is always closer in time to the age of the outcome.

In addition, we evaluated smoking during pregnancy as possible effect modifier by adding a multiplicative term to the models. In all analyses, we adjusted for pubertal stage and SES in a subgroup of participants with available data on these covariates (n=1381). We repeated all analyses using changes in BMI SDSs as predictors.

The individual parameters of the broken stick model were fitted as randomly varying slopes in a linear multilevel model by the S Plus 8.0 function "lme".[28] All other statistical analyses were performed in SPSS version 16.0 (SPSS, Chicago IL, USA). The level of statistical significance was set at $p<0.05$.

RESULTS

Our population consisted of 772 girls and 708 boys, with a mean (± SD) age at the last visit of 16.2 ± 0.7 years. All social classes were represented (22.2%, 48.2%, and 29.7% in low, middle and high SES categories, respectively); and 88.4% of the population was Caucasian. 11.9% of our population was overweight and 2.6% was obese (Table 1). Changes in weight SDS over time showed that participants who were overweight or obese at age 16.2 years started at a higher birth weight SDS (B=0.14; 95% CI, 0.09 – 0.19; $p<0.001$), then grew parallel to normal weight children until age 1 and gradually crossed weight centiles (Figure 1).

Changes in childhood weight SDS and adiposity in adolescence

Weight gain in the age periods between 1 and 15 years was significantly associated with higher BMI, sum of skinfolds, %BF and waist circumference at age 16.2 years (Table 2). Weight gain from birth to 0.5 and from 0.5 to 1 year was associated with lower anthropometric measurements at age 16.2 years, but not in all analyses significantly. We found a consistent pattern of large increases in explained variances of all outcome measures by adding weight gain from 2 to 4 and 4 to 7 years (Table 2). One SDS of weight gain during these periods was associated with increases of +0.82 to +1.47 SD in BMI, sum of skinfolds, %BF and waist circumference at age 16.2 years (all $p<0.001$). Weight gain from 2 to 4 and

Table 1. Sociodemographic and anthropometric characteristics according to sex; data refer to age 16.2 years unless otherwise indicated.

		All	Girls	Boys	Sex effect
	n				P-value
Age (yrs)	1480	16.2 ± 0.68	16.3 ± 0.70	16.2 ± 0.66	0.33
Smoking in pregnancy (% yes)*	1478	30.2	31.5	28.7	0.24
Pubertal stage (% in 3 categories)**	1381	15.8 / 28.3 / 55.9	0.7 / 0.4 / 98.9	32.9 / 59.9 / 7.3	<0.001
Weight (kg)	1480	62.9 (57.1 – 69.9)	60.7 (55.4 – 66.3)	65.5 (59.8 – 73.6)	<0.001
Height (cm)	1480	174.0 ± 9.0	168.8 ± 6.6	179.6 ± 7.7	<0.001
BMI (kg/m^2)	1480	20.77 (19.18 – 22.62)	21.24 (19.53 – 23.10)	20.32 (18.77 – 22.09)	<0.001
Overweight/obese (%)	1473	11.9 / 2.6	13.8 / 2.3	9.8 / 3.0	0.10
Sum of skinfold thicknesses (mm)	1464	47 (32 – 65)	59 (47 – 73)	33 (26 – 45)	<0.001
Body fat (%)	1433	28.3 ± 5.7	31.4 ± 4.5	24.9 ± 4.8	<0.001
Waist circumference (cm)	1458	73.8 (69.9 – 78.7)	73.9 (69.8 – 79.1)	73.6 (70.2 – 78.3)	0.94

All data are means ± SD or median (interquartile range) unless otherwise indicated.

* Based on a parental questionnaire.

** Measured by the Physical Development Scale questionnaire, divided into pre/early pubertal, midpubertal and late/post pubertal.

P-value from chi-square test for smoking in pregnancy, pubertal stage, and overweight or obese;
t test for age, height, and % body fat;
Mann-Whitney U test for weight, BMI, sum of skinfold thicknesses, and waist circumference.

4 to 7 years was associated with a higher risk of being overweight/obese at age 16.2 years (odds ratios (ORs) per SDS: 35.7 (95% confidence interval (95% CI), 18.0 – 70.9) and 24.8 (95% CI, 12.7 – 48.2), respectively). Weight gains between age 2 to 4 and 4 to 7 years were also associated with higher SBP, insulin, LDLC, triglycerides, and metabolic syndrome score (+0.31 to +0.73 SD); and with lower HDLC (-0.24 to -0.28 SD) (Supplemental tables 1a&b). Gains in the age period between 11 and 15 years were also associated with large increases in explained variance of these metabolic traits. After adjustment for current BMI SDS, estimates for all metabolic parameters were substantially reduced to nonsignificant effects.

The use of gain in BMI instead of weight yielded weaker, but significant results: +0.42 to +0.89 SD for adiposity measures (all p<0.001) (Supplemental table 2). One unit change in BMI SDS between age 4 and 7 years increased the risk of overweight/obesity at age 16.2 years 20-fold (OR, 20.5; 95% CI, 10.6 – 39.9).

Adjustment for pubertal stage and SES had only minor effects on the results (*see* Supplemental table 3 for the association between weight gain and BMI SDS). All results were also similar after exclusion of all non-Caucasian participants (n=171, 11.6%); and also after excluding the second child of all twin pairs (n=9, 0.6%).

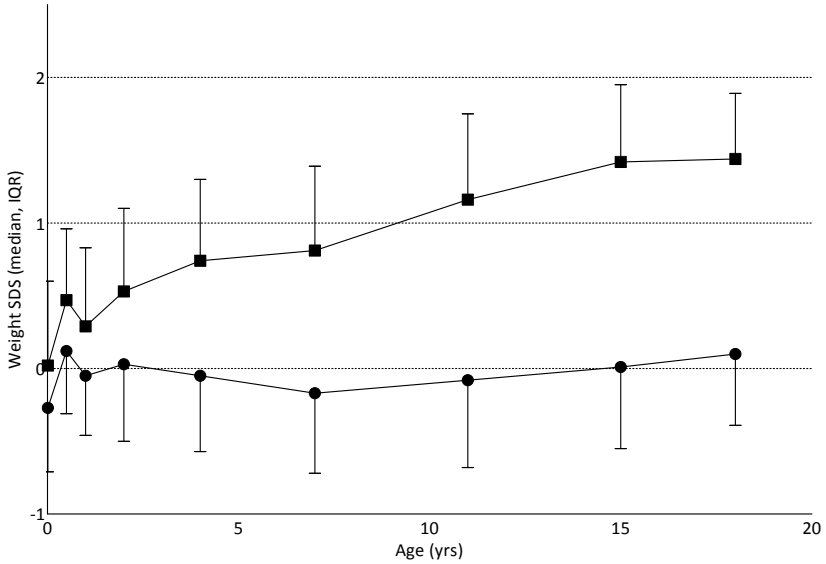

Figure 1. Weight SDS according to age in normal weight versus overweight/obese participants.
- ■ overweight/obese
- ● normal weight

Smoking during pregnancy

We evaluated smoking in pregnancy as possible effect modifier in the age periods in which changes in weight and BMI SDS were most strongly associated with anthropometric measurements at age 16.2 years. We found significant interaction terms in most of the models (Supplemental tables 4a&b). Additional adjustment for SES and pubertal stage did not affect the results.

We constructed separate models for adolescents who had been exposed to smoking during pregnancy and for adolescents who had not. In the former group, the influence of changes in weight and BMI on all anthropometric traits was consistently larger than in the latter group (Supplemental tables 4a&b). For example, each unit increase in weight SDS between 2 to 4 years was associated with an increase of 1.72 (95% CI, 1.46 – 1.98) in BMI SDS at age 16.2 years in adolescents whose mothers smoked during pregnancy, compared with 1.30 (95% CI, 1.11 – 1.49) in the other adolescents. The growth curve for overweight/obese participants at age 16.2 years whose mothers smoked during pregnancy, showed that they start with a relatively lower birth weight and grow fast between ages 2 to 7 years (Figure 2). However, adjustment for birth weight did not alter the results substantially.

Table 2. Associations (regression coefficients (B) and 95% confidence intervals) between weight SDS changes and anthropometric traits at age 16.2 years.

	Changes in weight SDS $B_{\text{weight change}}$ (95% CI) Δ *explained variance, p*			
Age period	**BMI SDS* (n=1480)**	**SF SDS* (n=1467)**	**%BF SDS (n=1433)**	**WC SDS* (n=1476)**
0 – 0.5 yr	-0.07 (-0.12 – -0.01) *0.003, 0.02*	-0.06 (-0.12 – -0.01) *0.003, 0.03*	-0.02 (-0.08 – 0.04) *<0.001, 0.49*	-0.07 (-0.12 – -0.01) *0.003, 0.02*
0.5 – 1 yr	-0.07 (-0.17 – 0.02) *0.001, 0.14*	-0.13 (-0.22 – -0.03) *0.004, 0.01*	-0.07 (-0.17 – 0.03) *0.001, 0.17*	-0.10 (-0.20 – -0.01) *0.003, 0.03*
1 – 2 yrs	0.78 (0.62 – 0.94) *0.048, <0.001*	0.53 (0.36 – 0.71) *0.022, <0.001*	0.60 (0.42 – 0.77) *0.028, <0.001*	0.65 (0.49 – 0.82) *0.034, <0.001*
2 – 4 yrs	1.47 (1.32 - 1.63) ***0.145, <0.001***	1.24 (1.07 – 1.42) ***0.101, <0.001***	1.30 (1.12 – 1.48) ***0.113, <0.001***	1.29 (1.14 – 1.45) ***0.112, <0.001***
4 – 7 yrs	1.11 (0.97 – 1.25) ***0.089, <0.001***	1.08 (0.92 – 1.24) ***0.083, <0.001***	1.18 (1.02 – 1.34) ***0.101, <0.001***	0.82 (0.57 – 0.96) ***0.048, <0.001***
7 – 11 yrs	0.47 (0.36 – 0.57) *0.023, <0.001*	0.56 (0.43 – 0.68) *0.033, <0.001*	0.61 (0.48 – 0.73) *0.04, <0.001*	0.19 (0.08 – 0.31) *0.004, <0.001*
11 – 15 yrs	0.99 (0.88 – 1.10) *0.061, <0.001*	0.79 (0.64 – 0.94) *0.038, <0.001*	0.67 (0.51 – 0.83) *0.027, <0.001*	0.83(0.70 – 0.96) *0.044, <0.001*

BMI SDS = body mass index SD score; SF SDS = sum of skinfolds SD score; %BF SDS = percentage body fat SD score; WC SDS = waist circumference SD score.

B's (95% CI), explained variances, and p-values are reported from multiple linear regression analyses adjusted for weight at the end of the age period.

Large changes in explained variances and corresponding age periods are in bold.

* Ln-transformed before calculation of SD scores to obtain a better approximation of the normal distribution.

DISCUSSION

We assessed the influence of changes in weight and BMI SDS on adolescent overweight. We found that particularly changes in weight and BMI SDS between age 2 to 4 and age 4 to 7 years were associated with increased SD scores of BMI, sum of skinfolds, %BF and waist circumference at age 16.2 years, with a substantially increased risk of being overweight or obese at age 16.2 years, and with associated metabolic traits. In addition, gains between 11 and 15 years had a strong influence on adiposity associated metabolic characteristics, specifically SBP, insulin, HDLC, LDLC, triglycerides, and a metabolic syndrome score. The effect of weight gain on these characteristics was significantly reduced after correction for current BMI SDS.

Our study comprises a large range in age, yielding findings that contrast with some earlier studies, but confirm many others. Some earlier studies that generally evaluated only infant growth found positive associations with subsequent adiposity,[2,4] whereas we

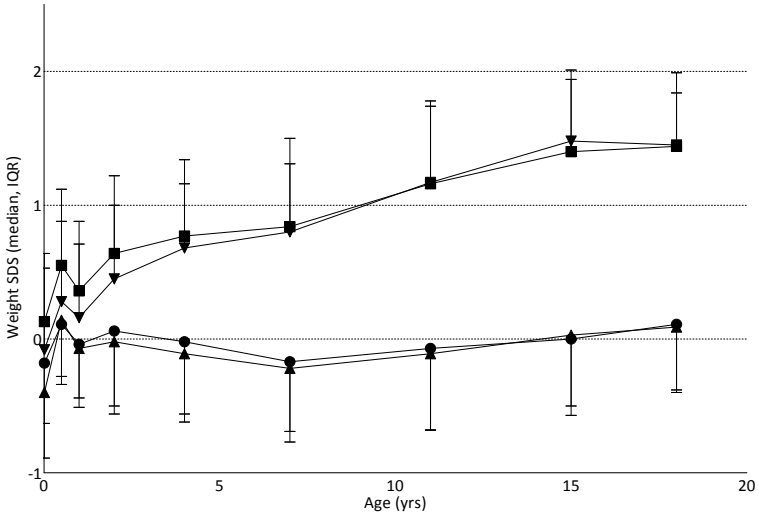

Figure 2. Weight SDS according to age in overweight/obese versus normal weight participants whose mothers did or did not smoke during pregnancy.

■ overweight/obese no smoking
▼ overweight/obese smoking
● normal weight no smoking
▲ normal weight smoking

found that weight gains in infancy were associated with lower BMI, sum of skinfolds, %BF, and waist circumference SD scores, although effect sizes were small and not consistently significant. Our findings are consistent with other reports assessing both infant and childhood growth.[29-31] Childhood growth (using varying definitions of age 21 months to 5 years, age 3 to 6 years, and age 3 to 7 years) showed a stronger association than infant growth with adult BMI, fatness, and waist circumference. Moreover, a Finnish study on growth curves from birth to age 13 years showed that growth started to deviate at age 2-3 for children who were overweight at age 13 years.[32] A study on adult outcomes using a similar methodology as ours, identified the age period of 2 to 6 years as the most critical in the development of adult overweight.[33] Our findings are also in line with the null findings reported by Wells and colleagues on the association between infancy weight gain and fatness,[34] and with the previously described 'gap' in the association between growth and subsequent BMI for weight gain between ages 6 to 24 months.[29,35,36] Finally, adolescents who were overweight at age 16.2 years already started with a higher birth weight. This is consistent with previous studies that showed an association between high birth weight and increased risk of subsequent overweight.[37,38]

Smoking during pregnancy modified the association between childhood weight gain and adolescent adiposity. In adolescents who had been exposed to smoking during pregnancy, changes in weight and BMI SDS were associated with larger increases in adiposity related measures at age 16.2 years than in adolescents who were not exposed, independent of SES. We constructed separate growth curves for overweight adolescents who had or had not been exposed to smoking during pregnancy (Figure 2). Overweight adolescents who had been exposed had a relatively low birth weight and catch-up growth between ages 2 and 7 years. From age 7 years, their growth curve was similar to that of overweight adolescents who were not exposed. Adjustment for birth weight did not change these results, suggesting that birth weight does not affect the modifying effect of smoking during pregnancy. Others have found a similar influence of smoking during pregnancy, also independent of SES,[10] which renders a socioeconomic explanation for these and our findings unlikely. We cannot rule out the possibility that our findings are due to residual confounding, for example unhealthy diets or lower physical activity levels among children whose parents smoke.[39]

Main strengths of our study are the multiple measurements of weight and height from early infancy to adolescence available in a large contemporary cohort that has been thoroughly assessed with regard to measures of overall and abdominal overweight at age 16.2 years and possible confounders including SES and smoking during pregnancy. A potential limitation is that these measurements of weight and height were performed by various professionals in the well-child clinics. This could result in increased measurement error, which might lead to underestimation of the strength of the associations. However, others have described robust findings using such routine examinations.[40,41] Secondly, we used SDSs obtained from cross-sectional data to model our longitudinal data, which does have its limitations. It could explain the fact that a large part of the growth curve of the normal weight participants is situated below SD=0.

In conclusion, we found that increases in weight and BMI SDS between ages 2 to 7 years predispose to overall and abdominal adiposity in adolescence. In adolescents whose mothers smoked during pregnancy, the influence of weight gain during these years is more pronounced. Our findings support the idea that preventive strategies should commence early, at the age of 2 years; and that in focusing on high risk groups, they should especially target children whose mothers smoked during pregnancy. This offers important clues to influence the overweight epidemic, even though the effectiveness of interventions in this age-period requires additional study.

REFERENCES

1. Dietz WH. Critical periods in childhood for the development of obesity. Am J Clin Nutr 1994;59(5):955-9.
2. Baird J, Fisher D, Lucas P, Kleijnen J, Roberts H, and Law C. Being big or growing fast: systematic review of size and growth in infancy and later obesity. BMJ 2005;331(7522):929.
3. Monteiro PO and Victora CG. Rapid growth in infancy and childhood and obesity in later life--a systematic review. Obes Rev 2005;6(2):143-54.
4. Ong KK and Loos RJ. Rapid infancy weight gain and subsequent obesity: systematic reviews and hopeful suggestions. Acta Paediatr 2006;95(8):904-8.
5. Whitaker RC, Pepe MS, Wright JA, Seidel KD, and Dietz WH. Early adiposity rebound and the risk of adult obesity. Pediatrics 1998;101(3):E5.
6. Gardner DS, Hosking J, Metcalf BS, Jeffery AN, Voss LD, and Wilkin TJ. Contribution of early weight gain to childhood overweight and metabolic health: a longitudinal study (EarlyBird 36). Pediatrics 2009;123(1):e67-73.
7. Lobstein T, Baur L, and Uauy R. Obesity in children and young people: a crisis in public health. Obes Rev 2004;5 Suppl 1:4-104.
8. Karaolis-Danckert N, Buyken AE, Bolzenius K, Perim de Faria C, Lentze MJ, and Kroke A. Rapid growth among term children whose birth weight was appropriate for gestational age has a longer lasting effect on body fat percentage than on body mass index. Am J Clin Nutr 2006;84(6):1449-55.
9. Stettler N. Nature and strength of epidemiological evidence for origins of childhood and adulthood obesity in the first year of life. Int J Obes (Lond) 2007;31(7):1035-43.
10. Karaolis-Danckert N, Buyken AE, Kulig M et al. How pre- and postnatal risk factors modify the effect of rapid weight gain in infancy and early childhood on subsequent fat mass development: results from the Multicenter Allergy Study 90. Am J Clin Nutr 2008;87(5):1356-64.
11. Huisman M, Oldehinkel AJ, de Winter A et al. Cohort profile: the Dutch 'TRacking Adolescents' Individual Lives' Survey'; TRAILS. Int J Epidemiol 2008;37(6):1227-35.
12. Brugman E, Reijneveld SA, Verhulst FC, and Verloove-Vanhorick SP. Identification and management of psychosocial problems by preventive child health care. Arch Pediatr Adolesc Med 2001;155(4):462-9.
13. Reijneveld SA, van der Wal MF, Brugman E, Sing RA, and Verloove-Vanhorick SP. Infant crying and abuse. Lancet 2004;364(9442):1340-2.
14. Reijneveld SA, Brugman E, Verhulst FC, and Verloove-Vanhorick SP. Identification and management of psychosocial problems among toddlers in Dutch preventive child health care. Arch Pediatr Adolesc Med 2004;158(8):811-7.
15. Cole TJ, Bellizzi MC, Flegal KM, and Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000;320(7244):1240-3.
16. Deurenberg P, van der KK, Leenen R, Weststrate JA, and Seidell JC. Sex and age specific prediction formulas for estimating body composition from bioelectrical impedance: a cross-validation study. Int J Obes 1991;15(1):17-25.
17. Jaspers M, de Meer G, Verhulst FC, Ormel J, and Reijneveld SA. Limited validity of parental recall on pregnancy, birth, and early childhood at child age 10 years. J Clin Epidemiol 2010;63(2):185-91.
18. Carskadon MA and Acebo C. A self-administered rating scale for pubertal development. J Adolesc Health 1993;14(3):190-5.
19. Amone-P'Olak K, Burger H, Ormel J, Huisman M, Verhulst FC, and Oldehinkel AJ. Socioeconomic position and mental health problems in pre- and early-adolescents: the TRAILS study. Soc Psychiatry Psychiatr Epidemiol 2009;44(3):231-8.
20. Growth analyser 3. Application. Ed. Dutch Growth Foundation, PO Box 23068, 3001 KB, Rotterdam, The Netherlands. 2003.

21. Fredriks AM, Van Buuren S, Burgmeijer RJ et al. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000;47(3):316-23.
22. Dennison BA, Edmunds LS, Stratton HH, and Pruzek RM. Rapid infant weight gain predicts childhood overweight. Obesity (Silver Spring) 2006;14(3):491-9.
23. Reilly JJ, Armstrong J, Dorosty AR et al. Early life risk factors for obesity in childhood: cohort study. BMJ 2005;330(7504):1357.
24. Vogels N, Posthumus DL, Mariman EC et al. Determinants of overweight in a cohort of Dutch children. Am J Clin Nutr 2006;84(4):717-24.
25. Eriksson JG, Osmond C, Kajantie E, Forsen TJ, and Barker DJ. Patterns of growth among children who later develop type 2 diabetes or its risk factors. Diabetologia 2006;49(12):2853-8.
26. Ruppert D, Wand MP, and Carroll RJ. Semiparametric regression. Cambridge: Cambridge University Press; 2003.
27. Brage S, Wedderkopp N, Ekelund U et al. Features of the metabolic syndrome are associated with objectively measured physical activity and fitness in Danish children: the European Youth Heart Study (EYHS). Diabetes Care 2004;27(9):2141-8.
28. Pinheiro JC and Bates DM. Mixed Effects Models in S and S-Plus. Springer, New York; 2002.
29. McCarthy A, Hughes R, Tilling K, Davies D, Smith GD, and Ben-Shlomo Y. Birth weight; postnatal, infant, and childhood growth; and obesity in young adulthood: evidence from the Barry Caerphilly Growth Study. Am J Clin Nutr 2007;86(4):907-13.
30. Corvalan C, Gregory CO, Ramirez-Zea M, Martorell R, and Stein AD. Size at birth, infant, early and later childhood growth and adult body composition: a prospective study in a stunted population. Int J Epidemiol 2007;36(3):550-7.
31. Ekelund U, Ong K, Linne Y et al. Upward weight percentile crossing in infancy and early childhood independently predicts fat mass in young adults: the Stockholm Weight Development Study (SWEDES). Am J Clin Nutr 2006;83(2):324-30.
32. Lagstrom H, Hakanen M, Niinikoski H et al. Growth patterns and obesity development in overweight or normal-weight 13-year-old adolescents: the STRIP study. Pediatrics 2008;122(4):e876-83.
33. De Kroon ML, Renders CM, Van Wouwe JP, Van Buuren S, and Hirasing RA. The Terneuzen birth cohort: BMI changes between 2 and 6 years correlate strongest with adult overweight. PLoS One 2010;5(2):e9155.
34. Wells JC, Hallal PC, Wright A, Singhal A, and Victora CG. Fetal, infant and childhood growth: relationships with body composition in Brazilian boys aged 9 years. Int J Obes (Lond) 2005;29(10):1192-8.
35. Botton J, Heude B, Maccario J, Ducimetiere P, and Charles MA. Postnatal weight and height growth velocities at different ages between birth and 5 y and body composition in adolescent boys and girls. Am J Clin Nutr 2008;87(6):1760-8.
36. Chomtho S, Wells JC, Williams JE, Davies PS, Lucas A, and Fewtrell MS. Infant growth and later body composition: evidence from the 4-component model. Am J Clin Nutr 2008;87(6):1776-84.
37. Oken E and Gillman MW. Fetal origins of obesity. Obes Res 2003;11(4):496-506.
38. Monteiro PO, Victora CG, Barros FC, and Monteiro LM. Birth size, early childhood growth, and adolescent obesity in a Brazilian birth cohort. Int J Obes Relat Metab Disord 2003;27(10):1274-82.
39. Leary SD, Smith GD, Rogers IS, Reilly JJ, Wells JC, and Ness AR. Smoking during pregnancy and offspring fat and lean mass in childhood. Obesity (Silver Spring) 2006;14(12):2284-93.
40. Bundred P, Kitchiner D, and Buchan I. Prevalence of overweight and obese children between 1989 and 1998: population based series of cross sectional studies. BMJ 2001;322(7282):326-8.
41. Kinra S, Baumer JH, and Davey SG. Early growth and childhood obesity: a historical cohort study. Arch Dis Child 2005;90(11):1122-7.

SUPPLEMENTARY TABLES

Supplemental table 1a. Associations (regression coefficients (B) and 95% confidence intervals) between weight SDS changes and metabolic traits at age 16.2 years.

	Changes in weight SDS $B_{\text{weight change}}$ (95% CI) Δ *explained variance, p*			
Age period	**SBP SDS***	**DBP SDS***	**glucose SDS**	**insulin SDS***
0 – 0.5 yr	0.02 (-0.03 – 0.08) *<0.001, 0.42*	0.04 (-0.01 – 0.10) *0.002, 0.13*	-0.01 (-0.08 – 0.06) *<0.001, 0.88*	-0.02 (-0.09 – 0.05) *<0.001, 0.59*
0.5 – 1 yr	-0.04 (-0.13 – 0.06) *<0.001, 0.42*	-0.03 (-0.13 – 0.06) *<0.001, 0.49*	0.08 (-0.04 – 0.19) *0.002, 0.20*	-0.08 (-0.19 – 0.04) *0.002, 0.20*
1 – 2 yrs	0.26 (0.08 – 0.44) *0.005, 0.01*	0.08 (-0.10 – 0.26) *0.001, 0.38*	0.10 (-0.12 – 0.31) *0.001, 0.38*	0.16 (-0.05 – 0.37) *0.002, 0.13*
2 – 4 yrs	0.48 (0.29 – 0.68) ***0.015, <0.001***	0.15 (-0.05 – 0.35) *0.002, 0.13*	0.14 (-0.10 – 0.38) *0.001, 0.27*	0.73 (0.49 – 0.96) ***0.035, <0.001***
4 – 7 yrs	0.35 (0.16 – 0.53) ***0.009, <0.001***	0.15 (-0.04 – 0.34) *0.002, 0.12*	0.01 (-0.21 – 0.23) *<0.001, 0.94*	0.61 (0.39 – 0.83) ***0.029, <0.001***
7 – 11 yrs	0.09 (-0.06 – 0.24) *0.001, 0.25*	0.04 (-0.11 – 0.20) *<0.001, 0.58*	-0.02 (-0.21 – 0.16) *<0.001, 0.80*	0.35 (0.17 – 0.53) *0.014, <0.001*
11 – 15 yrs	0.31 (0.11 – 0.51) ***0.006, 0.002***	-0.04 (-0.24 – 0.17) *<0.001, 0.72*	0.32 (0.07 – 0.58) ***0.006, 0.01***	0.70 (0.46 – 0.94) ***0.029, <0.001***

SBP SDS = systolic blood pressure SD score; DBP SDS = diastolic blood pressure SD score.

B's (95% CI), explained variances, and p-values are reported from multiple linear regression analyses adjusted for weight at the end of the period.

Large changes in explained variances and corresponding age periods are in bold.

* Ln-transformed before calculation of SD scores to obtain a better approximation of the normal distribution.

Supplemental table 1b. Associations (B (95% CI)) between weight SDS changes and metabolic traits at age 16.2 years.

	Changes in weight SDS $B_{\text{weight change}}$ (95% CI) *Δ explained variance, p*			
Age period	**HDLC SDS***	**LDLC SDS***	**Triglyceride SDS**	**Metabolic syndrome score***
0 – 0.5 yr	0.02 (-0.05 – 0.09) *<0.001, 0.56*	0.02 (-0.04 – 0.09) *<0.001, 0.53*	0.01 (-0.06 – 0.08) *<0.001, 0.73*	-0.01 (-0.05 – 0.03) *<0.001, 0.68*
0.5 – 1 yr	-0.01 (-0.13 – 0.10) *<0.001, 0.82*	-0.12 (-0.23 – 0.00) *0.004, 0.05*	-0.12 (-0.24 – -0.01) *0.004, 0.04*	-0.03 (-0.09 – 0.03) *0.001, 0.34*
1 – 2 yrs	-0.07 (-0.28 – 0.14) *<0.001, 0.53*	0.04 (-0.18 – 0.25) *<0.001, 0.74*	0.07 (-0.14 – 0.28) *<0.001, 0.51*	0.18 (0.07 – 0.29) *0.009, 0.002*
2 – 4 yrs	-0.24 (-0.48 – 0.00) *0.004, 0.05*	0.26 (0.02 – 0.50) ***0.004, 0.03***	0.27 (0.03 – 0.50) ***0.005, 0.03***	0.49 (0.36 – 0.61) ***0.053, <0.001***
4 – 7 yrs	-0.28 (-0.50 – -0.06) ***0.006, 0.01***	0.22 (-0.002 – 0.45) ***0.004, 0.05***	0.19 (-0.03 – 0.41) *0.003, 0.10*	0.37 (0.26 – 0.48) ***0.035, <0.001***
7 – 11 yrs	-0.15 (-0.33 – 0.03) *0.002, 0.11*	0.21 (0.03 – 0.39) ***0.005, 0.03***	0.09 (-0.09 – 0.27) *0.001, 0.32*	0.16 (0.06 – 0.25) *0.009, 0.001*
11 – 15 yrs	-0.28 (-0.53 – -0.03) ***0.005, 0.03***	0.21 (0.03 – 0.39) ***0.010, 0.001***	0.38 (0.13 – 0.63) ***0.009, 0.03***	0.48 (0.36 – 0.60) ***0.048, <0.001***

HDLC SDS = high density lipoprotein cholesterol SD score; LDLC SDS = low density lipoprotein cholesterol SD score. B's (95% CI), explained variances, and p-values are reported from multiple linear regression analyses adjusted for weight at the start of the period.

Large changes in explained variances and corresponding age periods are in bold.

* Ln-transformed before calculation of SD scores to obtain a better approximation of the normal distribution.

Supplemental table 2. Associations between BMI SDS changes and anthropometric traits at age 16.2 years.

	Changes in BMI SDS $B_{\text{weight change}}$ (95% CI) Δ *explained variance, p*			
Age period	**BMI SDS* (n=1480)**	**SF SDS* (n=1467)**	**%BF SDS (n=1433)**	**WC SDS* (n=1476)**
0 – 0.5 yr	-0.19 (-0.26 – -0.11) *0.016, <0.001*	-0.14 (-0.21 – -0.06) *0.008, <0.001*	-0.08 (-0.16 – -0.01) *0.003, 0.03*	-0.16 (-0.23 – -0.08) *0.011, <0.001*
0.5 – 1 yr	-0.13 (-0.21 – -0.04) *0.006, 0.003*	-0.18 (-0.27 – -0.09) *0.011, <0.001*	-0.13 (-0.22 – -0.04) *0.006, 0.004*	-0.12 (-0.21 – -0.04) *0.005, <0.001*
1 – 2 yrs	0.33 (0.22 – 0.44) *0.021, <0.001*	0.27 (0.15 – 0.38) *0.013, <0.001*	0.28 (0.17 – 0.39) *0.015, <0.001*	0.25 (0.14 – 0.36) *0.012, <0.001*
2 – 4 yrs	0.47 (0.39 – 0.56) ***0.044, <0.001***	0.42 (0.31 – 0.52) ***0.033 <0.001***	0.43 (0.33 – 0.54) ***0.036, <0.001***	0.45 (0.35 – 0.55) ***0.039, <0.001***
4 – 7 yrs	0.79 (0.69 – 0.90) ***0.056, <0.001***	0.87 (0.74 – 1.01) ***0.067, <0.001***	0.89 (0.75 – 1.02) ***0.071, <0.001***	0.69 (0.56 – 0.82) ***0.042, <0.001***
7 – 11 yrs	0.22 (0.13 – 0.31) *0.005, <0.001*	0.50 (0.38 – 0.62) *0.023, <0.001*	0.47 (0.35 – 0.59) *0.021, <0.001*	0.18 (0.06 – 0.31) *0.003, 0.004*
11 – 15 yrs	0.71 (0.63 – 0.79) *0.030, <0.001*	0.54 (0.39 – 0.68) *0.017, <0.001*	0.45 (0.31 – 0.60) *0.012, <0.001*	0.047 (0.32 – 0.61) *0.013, <0.001*

BMI SDS = body mass index SD score; SF SDS = sum of skinfolds SD score; %BF SDS = percentage body fat SD score; WC SDS = waist circumference SD score.

B's (95% CI), explained variances, and p-values are reported from multiple linear regression analyses adjusted for BMI at the end of the period.

Large changes in explained variances and corresponding age periods are in bold.

* Ln-transformed before calculation of SD scores to obtain a better approximation of the normal distribution.

Supplemental table 3. Associations between weight SDS changes and BMI at age 16.2 years with stepwise adjustment for possible confounders.

	BMI SDS (n=1381) $B_{weight\ change}$ (95% CI) *Δ explained variance, p*	
Age period	**Adjusted for weight SDS at end of age period**	**Adjusted for pubertal stage[*] and socioeconomic status[**]**
0 – 0.5 yr	-0.05 (-0.11 – 0.004) *0.002, 0.07*	-0.06 (-0.12 – -0.01) *0.003, 0.03*
0.5 – 1 yr	-0.04 (-0.13 – 0.06) *<0.001, 0.45*	-0.04 (-0.14 – 0.05) *<0.001, 0.40*
1 – 2 yrs	0.81 (0.64 – 0.98) *0.054, <0.001*	0.79 (0.63 – 0.96) *0.052, <0.001*
2 – 4 yrs	1.50 (1.34 – 1.66) ***0.152, <0.001***	1.46 (1.30 – 1.62) ***0.142, <0.001***
4 – 7 yrs	1.13 (0.99 – 1.28) ***0.094, <0.001***	1.09 (0.94 – 1.23) ***0.085, <0.001***
7 – 11 yrs	0.50 (0.39 – 0.61) *0.028, <0.001*	0.47 (0.36 – 0.58) *0.024, <0.001*
11 – 15 yrs	0.95 (0.83 – 1.06) *0.059, <0.001*	0.94 (0.82 – 1.05) *0.058, <0.001*

BMI SDS = body mass index SD score; BMI was ln-transformed before calculation of SD scores to obtain a better approximation of the normal distribution.

Large changes in explained variances and corresponding age periods are in bold.

Explained variances, B's (95% CI), and p-values are reported from multiple linear regression analyses.

[*] Physical Development Scale questionnaire, divided into pre/early pubertal, midpubertal and late/post pubertal.

[**] Based on questionnaires and classified as low, medium, and high socioeconomic status.

Supplemental table 4a. Smoking during pregnancy as potential effect modifier in the associations between weight changes and anthropometric traits at age 16.2 years.

	BMI SDS* **(n=1593)**	**SF SDS*** **(n=1573)**	**%BF SDS** **(n=1543)**	**WC SDS*** **(n=1589)**
weight change 2 – 4 yrs (SDS)				
$B_{interaction}$ (95% CI), p	0.42 (0.10 – 0.74), 0.01	0.28 (-0.08 – 0.64), 0.12	0.33 (-0.03 – 0.69), 0.08	0.39 (0.07 – 0.72), 0.02
$B_{weight\ change}$ (95% CI), p in model for non-smoking exposure	1.30 (1.11 – 1.49), <0.001	1.12 (0.91 – 1.33), <0.001	1.16 (0.94 – 1.38), <0.001	1.13 (0.94 – 1.32), <0.001
$B_{weight\ change}$ (95% CI), p in model for smoking exposure	1.72 (1.46 – 1.98), <0.001	1.40 (1.11 – 1.69), <0.001	1.49 (1.19 – 1.78), <0.001	1.53 (1.26 – 1.79), <0.001
weight change 4 – 7 yrs (SDS)				
$B_{interaction}$ (95% CI), p	0.22 (-0.07 – 0.50), 0.14	0.18 (-0.14 – 0.51), 0.27	0.07 (-0.27 – 0.40), 0.70	0.38 (0.08 – 0.68), 0.01
$B_{weight\ change}$ (95% CI), p in model for non-smoking exposure	1.01 (0.84 – 1.18), <0.001	1.00 (0.80 – 1.19), <0.001	1.13 (0.94 – 1.33), <0.001	0.66 (0.49 – 0.84), <0.001
$B_{weight\ change}$ (95% CI), p in model for smoking exposure	1.22 (0.99 – 1.46), <0.001	1.18 (0.91 – 1.45), <0.001	1.20 (0.93 – 1.47), <0.001	1.05 (0.80 – 1.29), <0.001

BMI SDS = body mass index SD score; SF SDS = sum of skinfolds SD score; %BF SDS = percentage body fat SD score; WC SDS = waist circumference SD score.

B's (95% CI), and p-values are reported from multiple linear regression analyses adjusted for BMI at the end of the period.

Similar results were obtained after adjustment for pubertal stage and SES.

* Ln-transformed before calculation of SD scores to obtain a better approximation of the normal distribution.

Supplemental table 4b. Smoking during pregnancy as potential effect modifier in the associations between BMI changes and anthropometric traits at age 16.2 years.

	BMI SDS* **(n=1593)**	**SF SDS*** **(n=1573)**	**%BF SDS** **(n=1543)**	**WC SDS*** **(n=1589)**
BMI change 4 - 7 yrs (SDS)				
$B_{interaction}$ (95% CI), p	0.38 (0.15 – 0.61), 0.001	0.46 (0.16 – 0.76), 0.002	0.37 (0.08 – 0.67), 0.01	0.56 (0.27 – 0.85), <0.001
$B_{BMI\ change}$ (95% CI), p in model for non-smoking exposure	0.67 (0.55 – 0.79), <0.001	0.73 (0.57 – 0.89), <0.001	0.77 (0.61 – 0.93), <0.001	0.52 (0.36 – 0.68), <0.001
$B_{BMI\ change}$ (95% CI), p in model for smoking exposure	1.05 (0.85 – 1.25) <0.001	1.19 (0.94 – 1.45), <0.001	1.14 (0.89 – 1.40), <0.001	1.08 (0.83 – 1.33), <0.001

BMI SDS = body mass index SD score; SF SDS = sum of skinfolds SD score; %BF SDS = percentage body fat SD score; WC SDS = waist circumference SD score.

B's (95% CI), and p-values are reported from multiple linear regression analyses adjusted for BMI at the end of the period.

Similar results were obtained after adjustment for pubertal stage and SES.

* Ln-transformed before calculation of SD scores to obtain a better approximation of the normal distribution.